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Do short-term markers of treatment efficacy predict long-term sequelae of PID?

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Abstract

Objective—To assess whether short-term markers, often used to measure clinical cure after treatment for pelvic inflammatory disease (PID), predict sequelae of lack of pregnancy, recurrent PID, and chronic pelvic pain.

Study Design—Women with mild-to-moderate PID were assessed after treatment initiation at five days for tenderness (n=713) and at thirty days for tenderness, cervical infections and endometritis (n=298). Pregnancy, recurrent PID and chronic pelvic pain were evaluated after 84 months, on average.

Results—Pelvic tenderness at five and at thirty days significantly elevated the risk for developing chronic pelvic pain; tenderness at thirty days was also significantly associated with recurrent PID. However, pelvic tenderness at five and at thirty days were only modestly clinically predictive of chronic pelvic pain or recurrent PID (positive predictive values 22.1–66.9%). No short-term marker significantly influenced the likelihood of achieving a pregnancy.

Conclusion—Tenderness at 5 or 30 days did not accurately predict the occurrence of PID-related reproductive morbidities.

CONCISE—Tenderness at 5 or 30 days and microbiologic cure post-pelvic inflammatory disease treatment did not accurately predict long-term sequelae including chronic pelvic pain, fertility, and recurrence.

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Keywords

adnexitis; chlamydia; endometritis; treatment; prediction; recurrent PID; chronic pain; infertility

INTRODUCTION

Pelvic inflammatory disease (PID) is a common clinical condition consisting of ascending infection from the lower to upper genital tract. More than 750,000 women in the U.S. are diagnosed with PID annually.¹ The long-term sequelae of PID include infertility, ectopic pregnancy, recurrent PID and chronic pelvic pain.^{2–5} Costs of treating PID and its sequelae are estimated at about \$2 billion per year in the U.S.⁶

The most commonly used metrics for defining the success of regimens used to treat PID have been eradication of the underlying infection(s) and reduction of PID-related signs and symptoms. Microbiologic cure has been defined as an eradication of gonococcal and/or chlamydial cervicitis. Whereas the definition of clinical cure varies, it frequently includes improvement in tenderness and severity scores, resolution of fever, and normalization of white blood cell count.^{7–15} The timing of follow-up in measuring treatment success varies, ranging from assessment at the time of hospital discharge or antibiotic discontinuance to assessment three to five weeks post-therapy.¹⁵

However, short-term clinical and/or microbiologic cure does not preclude the occurrence of PID-related sequelae. In a study involving repeat laparoscopy, after successful treatment of chlamydia with cefoxitin and doxycycline, persistent tubal inflammation was found in eight of 11 women (73%).¹⁶ In other studies after antibiotic treatment for PID, rates of tubal scarring ranged from 33% to 45%.^{17–19} Persistence of endometritis was found in nine of twenty (45%) women successfully treated with minocycline.²⁰ Thus, despite treatment and clinical improvement, upper genital tract inflammation and scarring may persist. In general, little is known about the degree to which short-term markers commonly used in determining clinical and microbiologic success predict the long-term sequelae that contribute to the significant morbidity and decline in the quality of life after episodes of PID.^{4,21}

The PEACH study is a prospective U.S. study of reproductive morbidity among women post-PID. Follow-up duration averaged 84 months. The goal of this analysis is to evaluate whether short-term markers (tenderness at 5 days and tenderness at 30 days, cervical infection at 30 days, and endometrial pathology consistent with endometritis at 30 days) predict long-term morbidity (lack of pregnancy, chronic pelvic pain, and recurrent PID) among a cohort of US women with mild-to-moderate PID.

METHODS

Subjects

Methods of participant selection and recruitment, data collection, and follow-up have been described in detail elsewhere.^{22,23} Briefly, between March 1996 and February 1999 women ages 14–37 were recruited from emergency departments, clinics, and sexually transmitted disease units at seven major clinical sites in the eastern, southern, and central regions of the US. Human subject approval was obtained at each participating institution and all participants signed an informed consent. Eligibility was based on clinically generalizable criteria that included: 1) a history of pelvic discomfort for a period of 30 days or less, 2) findings of pelvic organ tenderness (uterine or adnexal) on bimanual examination, and 3) leukorrhea or mucopurulent cervicitis or both, and/or untreated, but documented gonococcal or chlamydial cervicitis. Leukorrhea was defined as white blood cells in excess of epithelial cells viewed

microscopically and mucopurulent cervicitis was defined by the presence of grossly yellow/green exudate on a cervical swab.

Participants were selected from 2941 women screened. Three hundred forty six women not meeting the inclusion criteria were excluded (11.8%). Additionally 1080 (36.7%) women were excluded on the basis of *a priori* criteria, including 141 (4.8%) due to pregnancy; 246 (8.4%) who had taken antimicrobial agents in the preceding 7 days; 248 (8.4%) with a previous hysterectomy or bilateral salpingectomy; 51 (1.7%) with an abortion, delivery, or gynecologic surgery in the preceding 14 days; 191 (6.5%) with suspected tuboovarian abscess or other condition necessitating surgery; 163 (5.5%) with an allergy to the study medication; 29 (1.0%) who were homeless, and 11 (0.4%) who vomited after a trial of antiemetic treatment, resulting in 1515 eligible women. Of these, 651 refused participation and of 864 women who were enrolled, 831 (54.9% of those eligible) were contacted at least once after randomization (described below). Included in this analysis are the 713 women with complete information at the five-day visit.

Treatment

Participants were randomly assigned to inpatient or outpatient treatment groups. The inpatient strategy consisted of intravenous cefoxitin (2g) and oral doxycycline (100g) for a 14 day course. Outpatient treatment consisted of a single intramuscular injection of cefoxitin (2g) plus probenecid (1g) followed by oral doxycycline (100g) twice daily for 14 days. Participants were advised to have their partners treated and to abstain from sexual intercourse until the completion of their partners' treatment. Because treatment assignment was not associated with reproductive outcomes,²² both treatment groups were combined into a single cohort.

Follow-up

Participants were monitored with in person visits at 5 and 30 days. Follow-up began in March 1996. Subsequent telephone follow-ups were conducted every 3 months during the first year post enrollment and then every 4 months until June, 2004, at which point we were in contact with and obtained self-reported follow-up information for 69.1% of the cohort, representing a mean follow-up time of 84 months.

Data Collection

Baseline data on demographic descriptors, gynecologic and reproductive history, lifestyle habits, and clinical aspects of the current illness were obtained by a standardized 20-minute interview conducted by study nurses at each center. Subsequent follow-ups elicited self-reported information about pelvic pain, pregnancies, and births, signs/symptoms of PID, sexually transmitted infections, contraceptive use, pattern of sexual intercourse, and health care utilization.

Gynecologic examinations were conducted at five and thirty days and included tenderness assessment using the 36-point scale developed by McCormack et al;²⁴ ascertainment of cervical swabs for *N. gonorrhoeae* cultures and *C. trachomatis* polymerase chain reaction (PCR) detection; collection of vaginal swabs for gram stain detection of bacterial vaginosis; and aspiration of the endometrium for detection of gonorrhea and chlamydia. A central reference laboratory performed the PCRs and gram stains, with gram stain results interpreted according to the Nugent criteria.²⁵ Endometritis was defined by a modification of the Kiviat criteria,^{26,27} wherein the presence of at least five neutrophils in the endometrial surface epithelium in the absence of menstrual endometrium, or at least two plasma cells in the endometrial stroma indicated endometritis.

Outcomes

The primary outcomes in this analysis were determined over the entirety of follow up and included: lack of pregnancy, recurrent PID and chronic pelvic pain. Pregnancy was defined by positive urine or blood test, or doctor's diagnosis. Recurrent PID was determined by self-report and verified whenever medical records were available. As previously reported, confirmation of recurrent PID was found in 76% of medical records that could be obtained and rates of recurrent PID by self-report and medical record review were similar.²² Chronic pelvic pain was measured on the Von Korff pain scale²⁸ and defined by at least two consecutive reports at least three months apart, i.e. reported over a minimum duration of six months.

Statistical Analysis

The Kaplan-Meier method was used to estimate cumulative incidence rates of pregnancy, recurrent PID and chronic pelvic pain during follow-up by presence or absence of each short-term marker (5-day tenderness, 30-day tenderness, cervical infection, endometritis) as well as the presence or absence of a summary variable consisting of 30-day tenderness, cervical infection OR endometritis. The outcome of lack of pregnancy was the inverse of the pregnancy rate result. Subjects who did not experience the outcome of interest were censored at the date of last follow-up. Based on the distribution of follow-up (mean 84 months), incidence rates at 6-years are presented to provide estimates with adequate precision. Cox proportional hazard regression analysis was used to estimate the adjusted hazard ratio of each outcome of interest by short-term marker status. Covariates selected for adjustment included those that were significantly associated with the exposure and outcome and those considered of clinical or biological relevance. The proportional hazards assumption of invariant relevant risk during follow-up was assessed and found to be satisfactory. Given 713 women with return visit assessment of tenderness at 5 days, the study provided 80% power with a two sided alpha to detect a hazard ratio of 0.71 for pregnancy, 1.38 for chronic pelvic pain, and 1.36 for recurrent PID. For return visit assessment of tenderness at 30 days (n=298), corresponding detectable hazard ratios were 0.52, 1.95, and 1.88.

RESULTS

The majority of women in the sample were black (73%), younger than age 25 (64%), and had no more than a high school education (74%). Nearly one third had a previous history of PID (29%) and a slightly higher percentage had a previous STD at baseline (36%) (Table I). Over half of the women had tenderness at five days (58%); approximately 19% had tenderness at 30 days, 5% had gonococcal and/or chlamydial cervicitis at 30 days, and 41% had endometritis at 30 days.

Although 713 women had complete data for the five day return visit, only 298 women had complete covariate and marker data at 30 days. The women who did not return for the 30 day visit were significantly ($p<0.05$) more likely to be 25 or older, and of race other than African American or white. There were no significant differences in educational status, history of PID, parity and baseline gonococcal/chlamydial status.

The 6-year cumulative incidence rate of chronic pelvic pain ranged from 40% to 67% among subgroups of women with and without the four short-term markers assessed (Table II). Among the 74 women with an absence of all four short-term markers, chronic pelvic pain occurred in 32.4%. In analyses adjusted for age, race, education, history of PID, and live births, tenderness at 30 days (adjusted HR 2.45, 95% CI: 1.56–3.85), and to a lesser extent, tenderness at five days (adjusted HR 1.32; 95% CI: 1.05–1.67), were significantly associated with the occurrence of chronic pelvic pain during follow-up. The three 30-day markers were not significantly correlated with each other, and we combined them into a single summary marker consisting

of any of tenderness, cervicitis, or endometritis; the summary marker was also significantly associated with occurrence of chronic pelvic pain (adjusted HR 1.55, 95% CI: 1.07–2.25). However, for all four short-term markers and for the summary marker, estimates of predictive value positive (PV⁺) and predictive value negative (PV[−]) for occurrence of chronic pelvic pain during six-year follow-up and ranged from 49% to 67% indicating suboptimal predictive performance (Table III).

For recurrent PID, the six-year incidence rate ranged from 21% to 39% by short-term marker status (Table II) and was 23.6% among the subset of women with none of the four short-term markers. Like chronic pelvic pain, tenderness at 30 days was significantly associated with risk of recurrent PID (adjusted HR 2.16, 95% CI: 1.15–4.04), whereas tenderness at five days, cervical infection at 30 days, and endometrial pathology consistent with endometritis at 30 days, and the summary marker were not associated with recurrent PID. The adjusted HR of 1.70 for cervical infection at 30 days and risk of recurrent PID was imprecise as there were only 14 women in this subgroup. Estimates of PV⁺ for recurrent PID were <40% for each of the 4 short-term markers and the summary marker (Table III), and more than 20% of all women who were negative on each of the short-term markers and the summary marker ultimately experienced recurrent PID during follow-up, again, indicating overall suboptimal predictive performance (Table III).

Finally, the majority of women achieved pregnancy during follow-up irrespective of short-term marker status (Table II). In adjusted analyses, none of the short-term markers were associated with the likelihood of achieving pregnancy and estimates of PV⁺ and PV[−] indicated suboptimal predictive performance.

These results were all similar for women who had cervical Chlamydia, cervical gonococcal and neither infection at baseline. For markers for which we had sufficient power to analyze interactions (all but cervical infection), we found no significant differences in the outcomes of recurrent PID or lack of pregnancy among women with and without a prior history of PID. However, women who reported having PID prior to baseline had a significantly lower risk of chronic pelvic pain related to endometritis at 30 days (interaction $p=0.01$) and to the summary marker (interaction $p=0.02$).

DISCUSSION

The success of treatment for PID is generally gauged by short-term clinical improvement and/or microbiologic cure. Our results show that these short-term markers (tenderness at 5 and 30 days; gonococcal/chlamydial cervicitis at 30 days; endometritis at 30 days) are not strongly predictive of the long-term sequelae from PID that treatment is trying to prevent. Although persistent tenderness significantly increased the occurrence of chronic pelvic pain and recurrent PID, positive predictive values were too low to make short-term tenderness a clinically meaningful intermediate for predicting these long-term outcomes. Moreover, cervicitis and endometritis were not significantly associated with chronic pelvic pain or PID, and none of the short-term measures were predictive of the ability to achieve pregnancy.

We considered several explanations for our findings. First, cervical infection status may not adequately represent upper genital tract inflammation such as fallopian tube infection.^{5,22,29} Cervical infection often exists in the absence of endometrial infection/inflammation resulting in a short-term marker that is a false positive. The converse is also true: in two studies, 3.7% to 10% of women were documented with positive upper genital tract chlamydial cultures, despite negative cervical culture at baseline.^{5,22} This has also been documented post-treatment for PID, where four of 16 women had positive endometrial cultures for chlamydia despite negative endocervical cultures after second and third generation cephalosporin treatment.²⁹

Thus, despite a negative test for thirty day cervical infection, women may have experienced a persistent infection in their upper genital tract that contributed to long-term sequelae.

Second, women who delay seeking treatment for PID for three days or more are at nearly a three fold increase in risk for impaired fertility,³⁰ suggesting that early treatment administration may be necessary to halt a complete mounting of the inflammatory response. Because the majority of women in the PEACH study presented with three or more days of pelvic pain (71%),²² they may have been at increased risk for long-term sequelae regardless of short-term treatment response.

Third, women may have had prior subclinical (silent) PID that resulted in tubal damage preceding the baseline episode. Prior PID may have contributed, independent of the short-term markers from the index diagnosis of PID, to adverse reproductive sequelae. In a macaque monkey model, repeated exposure to chlamydial infections produced a Th-1 type cytokine response that was associated with the progression to fibrosis and infertility.^{31–33} In a study by Soper et al., second look laparoscopy revealed that previous disease was strongly predictive of subsequent tubal damage.³⁴ One test of cervical infection at thirty-days might not capture the women who had repeated exposures sufficient to produce fibrosis and scarring. We did not find any statistically significant interaction between prior PID and the short-term markers in predicting outcomes of recurrent PID or lack of pregnancy. For the outcome of chronic pelvic pain, our results are counterintuitive and might represent the inclusion of women with diagnoses other than PID in the outcome of chronic pelvic pain.

Fourth, PID has a polymicrobial etiology and several non-chlamydial, non-gonococcal pathogens have been implicated, including *Mycoplasma hominis*, *Ureaplasma urealyticum*, bacterial vaginosis (independent of gonorrhoea or chlamydia), and *Mycoplasma genitalium*.^{5,34–36} Some of these pathogens (*M. hominis* and *U. urealyticum*) are largely resistant to tetracyclines, and may have persisted following PID treatment.³⁷ In a previous PEACH analysis, women with nongonococcal bacteria in the endometrium were more likely to have reproductive morbidity compared to women with endometrial gonococcal infection (infertility rates were: *N. gonorrhoeae* 13%, *C. trachomatis* 19%, anaerobic bacteria 22%, *U. urealyticum* 41% and *M. hominis* 54%).³⁸ Further, Brunham and colleagues demonstrated over a five to seven month follow-up, 54% of women with non-gonococcal infections had adverse reproductive outcomes, compared to none of the women with gonococcal PID.⁵ Thus, women in the study may have had non-gonococcal, non-chlamydial pathogens that resulted in long-term sequelae. Our data suggest that commonly-used short-term markers do not adequately reflect the underlying pathophysiology that leads some women to have adverse long-term outcomes while others do not.

We had previously shown that endometritis and upper genital tract infection were not associated with reduced pregnancy, recurrent PID, infertility, or chronic pelvic pain after one year of follow-up in the PEACH Study.³⁸ This analysis extends that finding to examine the associations between several short-term markers and sequelae related to PID after a mean of six years of follow-up. The study has several strengths. First, the prospective design allowed actual measurements of all outcomes. Second, the PEACH study had a long-follow up duration (average follow-up length 84 months) and a sizeable rate of retention (69.1%).²² Third, the study was generalizable, as it enrolled women with mild-to-moderate PID who comprise 90% of women with PID.³⁹ Fourth, standardized laboratory procedures minimized bias and misclassification.

One notable weakness is the diminution in sample size between the five and thirty day visit, with 713 women (out of 831) with complete five day return visit data, and only 298 women with complete covariate and marker data at thirty days. Lack of significant findings may have

resulted from a lack of power, particularly for the assessment of cervical infection at 30 days. The women who did not return for the thirty day visit were more likely to be 25 or older, and of race other than African American or white. There were no significant differences in educational status, history of PID, parity and baseline gonococcal/chlamydial status. A second weakness was the reliance on self-report to determine recurrent PID. However, as previously noted, we found 76% confirmation of recurrent PID in verified medical records.²² A final weakness was that only about half of participants had endometritis and/or upper genital tract infection (indicators of salpingitis); in women without the true condition, short-term markers would likely not correlate with long-term outcomes. However, as the cohort represents patients that are typically treated for PID, the lack of predictiveness of short-term markers remains generalizable to women seen in usual clinical practice.

Short-term intermediate endpoints are frequently used to determine clinical or microbiologic cure for PID. However, our results suggest that such markers are generally unrelated to long-term reproductive morbidity and even when significant associations exist, the accompanying positive and negative predictive values are less than optimal. When conducting treatment trials, and when counseling women about their long-term health risks, we can recommend no currently-accepted short-term marker to predict the occurrence of PID-related reproductive morbidity.

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Table I
Baseline Characteristics: Study Participants in PEACH

Baseline Characteristic	N (713)	%
Age		
≤ 19	178	25.0%
20–24	281	39.4%
≥ 25	254	35.6%
Race		
African American	523	73.4%
White	120	16.8%
Other	70	9.8%
Education		
< High School Graduate	262	36.7%
High School Graduate	268	37.6%
> High School Graduate	183	25.7%
History of PID [*]		
No	504	70.7%
Yes	209	29.3%
Live Births		
0	250	35.1%
1–2	342	48.0%
≥ 3	121	17.0%
Baseline GC or CT ^{**}		
None	442	63.8%
Any	251	36.2%
Tenderness 5 Days		
No	300	42.1%
Yes	413	57.9%
Tenderness 30 Days		
No	505	80.9%
Yes	119	19.1%
Endometritis 30 Days		
No	242	58.9%
Yes	169	41.1%
GC or CT Status 30 Days ^{***}		
None	408	94.9%
Any	22	5.1%

^{*} 6 women had missing information for history of PID

^{**} 21 women had missing information for baseline gonorrhea/chlamydia

^{***} 294 women had missing information for 30 day gonorrhea/chlamydia

Table II
Risk of Chronic Pelvic Pain, Recurrent PID and Pregnancy in Relation to Short-Term Marker Status

Short-Term Marker	N	Chronic Pelvic Pain Rate* HR** 95% CI	N	Recurrent PID Rate* HR** 95% CI	N	No Pregnancy Rate* HR** 95% CI
Tenderness at 5 days						
No	298	40.7	289	20.7	300	38.5
Yes	407	52.6	400	22.1	413	37.1

Tenderness at 30 days						
No	257	40.3	249	21.4	259	40.4
Yes	39	66.9	37	39.1	39	47.8

Cervical infection at 30 days						
No	282	42.9	272	23.2	284	41.9
Yes	14	64.3	14	30.8	14	29.5

Endometritis at 30 days						
No	177	41.0	169	23.9	178	47.0
Yes	119	48.9	117	23.5	120	32.3

Tenderness, cervicitis, or endometritis at 30 days						
No	148	35.0	142	21.5	149	48.0
Yes	148	53.8	144	26.2	149	34.1

* Cumulative incidence rate at 6-years of follow-up

** Adjusted for: age, race, education, history of PID and live births

*** Based on 298 women with completed information for the 30 day visit.

Table III
Performance Yield of Short-Term Markers on Long-Term Sequelae at 6- Years of Follow-up

Short-Term Marker	N	Chronic Pelvic Pain		Recurrent PID		No Pregnancy	
		PV ⁺	PV ⁻	PV ⁺	PV ⁻	PV ⁺	PV ⁻
Tenderness at 5 days	713						
Tenderness at 30 days	298	52.6%	59.3%	22.1%	79.3%	37.1%	61.5%
Cervical infection at 30 days	298	66.9%	59.7%	39.1%	78.6%	47.8%	59.6%
Endometritis at 30 days	298	64.3%	57.1%	30.8%	76.8%	29.5%	58.1%
Tenderness, cervicitis, or endometritis at 30 days	296	48.9%	59.0%	23.5%	76.1%	32.3%	53.0%
		53.8%	65.0%	26.2%	78.5%	34.1%	52.0%

PV⁺: Predictive value positive. PV⁻: Predictive value negative